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MAJOR ARTICLE

An Outbreak of Conjunctivitis Due to a Novel Unencapsulated *Streptococcus pneumoniae* among Military Trainees

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Background. Bacterial conjunctivitis usually occurs as sporadic cases; outbreaks are uncommon and usually are associated with school campuses. We report an outbreak of *Streptococcus pneumoniae* conjunctivitis at a military training facility.

Methods. An outbreak investigation was done. Each case of conjunctivitis was evaluated with an assessment tool including demographic and clinical data. Conjunctival swabs were obtained. Pneumococci underwent standard testing, including serotyping with the Quellung reaction, capsular staining, and multilocus sequence typing. Sequence types were compared with previous reported outbreak strains by construction of dendrograms. Carriage rates of *S. pneumoniae* were determined among previously undiagnosed case patients with conjunctivitis, and a case-control study was performed. Control measures included education to increase hand washing, distribution of alcohol-based hand gel, and prompt treatment of patients with conjunctivitis.

Results. During a 6-week period, 92 cases of conjunctivitis occurred among 3500 persons, with an attack rate of 1.75 cases per 100 person-months. Eighty cases (87%) were due to *S. pneumoniae;* 45 (49%) were confirmed, and 35 (38%) were probable. Ten percent of recruits surveyed carried the outbreak strain. Twenty-two percent self-reported symptoms consistent with conjunctivitis during the outbreak period; sharing washcloths was associated with conjunctivitis (odds ratio, 11.7; $P = .03$). The causative organism was resistant to azithromycin but susceptible to telithromycin. The outbreak strain was an unencapsulated *S. pneumoniae* that has not been previously described; it was most closely related to the sequence type causing the Dartmouth College (Hanover, NH) outbreak of conjunctivitis in 2002.

Conclusions. We report a conjunctivitis outbreak among military trainees caused by a novel, unencapsulated strain of *S. pneumoniae.*

Bacterial conjunctivitis is caused by a variety of gram-positive and -negative organisms, including *Haemophilus influenzae, Staphylococcus aureus, Streptococcus pneumoniae, Chlamydia trachomatis, Neisseria gonorrhoeae,* and gram-positive anaerobes [1, 2]. Although *S. pneumoniae* is a frequent cause of sporadic conjunctivitis in all age groups, outbreaks caused by this organism are infrequent and usually linked to college residences [3, 4]. We report an outbreak of *S. pneumoniae* conjunctivitis among military trainees and discuss the clinical and molecular characteristics of a novel outbreak strain.

METHODS

An increase in the number of conjunctivitis cases was noted at a military training site in San Diego, California, during the first week of December 2003. Initial cultures of eye secretions suggested *S. pneumoniae* as the causative organism. An outbreak investigation was initiated on 5 December to determine the extent of the outbreak, confirm the cause, and implement preventive strategies. The setting of the outbreak was a military base in San Diego, with 3500 recruits living in close proximity during an 11-week training period. Recruits received the pneumococcal vaccine (polyvalent pneumovax 23; Merck) and influenza vaccine on arrival to the base

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(training day 1). Traditionally, recruits receive intramuscular benzathine penicillin every 4 weeks for prophylaxis against group A streptococci; however, because of an increase in respiratory infections several months earlier, recruits were instead receiving weekly 1-g doses of oral azithromycin.

Each potential case was evaluated with a standard conjunctivitis assessment tool including demographic, clinical, and physical examination data. Laboratory testing included culture of conjunctival swabs for bacterial and viral (adenovirus) pathogens. Isolates identified as *S. pneumoniae* underwent bile solubility and optochin susceptibility testing, serotyping with the Quellung reaction, capsular staining, and multilocus sequence typing [5]. Multilocus sequence types were initially aligned with DNAStar. Dendrograms were constructed by the unweighted pair-group method with arithmetic averages and the Jukes-Cantor correction performed by molecular evolutionary genetics analysis software [6]. In addition, an isolate of *S. pneumoniae* from a conjunctivitis outbreak in 1980 in this recruit camp was acquired and compared by use of this same battery of testing. Antimicrobial susceptibility testing was done by broth microdilution for penicillin, erythromycin, telithromycin, trimethoprim-sulfamethoxazole, clindamycin, tetracycline, levofloxacin, ceftriaxone, and vancomycin [7]. The Etest method (AB Biodisk) was used to determine azithromycin susceptibilities. WBC counts were determined and chest radiographs were done for select case patients as clinically indicated. Treatment with an ophthalmologic antimicrobial agent was given on the basis of provider preference.

A confirmed case of pneumococcal conjunctivitis was defined as conjunctivitis in any recruit or staff member occurring between 21 November and 31 December 2003 with a culture from eye secretions positive for *S. pneumoniae*. A probable case was defined as conjunctivitis with no pathogenic organism identified or no culture sample obtained. Conjunctivitis due to an alternative cause was defined as a case with isolation of a different pathogenic organism known to be associated with conjunctivitis.

Carriage rates of *S. pneumoniae* and cases of previously undiagnosed, self-reported conjunctivitis among recruits were determined by throat cultures and risk factor surveys among 151 recruits from the training group with the most clinical cases of conjunctivitis. Laboratory results were matched with questionnaire data.

The outbreak was controlled through education of the staff and recruits on preventive measures such as hand washing; alcohol-based hand gels were used. Patients with conjunctivitis were immediately referred to the medical clinic and treated with a topical antibiotic; follow-up in the clinic was required to ensure resolution. Daily review of all conjunctivitis cases was done until the outbreak abated.

"Baseline" rates of conjunctivitis were assessed by reviewing outpatient data records, including all ICD9-CM *(International Classification of Diseases, 9th edition, Clinical Modification)* diagnoses, from this recruit medical clinic between 1999 and 2001. Recruit population data allowed the calculation of the number of conjunctivitis cases per 100 person-months over this period.

Statistical analysis included descriptive data of the cases, and comparisons were made between the etiologic agents by use of Fisher's exact and *t* tests. Statistical analyses of the risk factors for both conjunctivitis and *S. pneumoniae* carriage were done with SPSS software.

RESULTS

Ninety-two cases of conjunctivitis were diagnosed among 3500 recruits between 21 November and 31 December 2003, for an overall attack rate of 1.75 cases per 100 person-months (figure 1). Ninety cases (98%) were among recruits, and 2 were among staff. In the most affected unit, 26 cases occurred among 400 recruits, for an attack rate of 4.3 cases per 100 person-months. Historical rates of conjunctivitis, averaged over the years 1999–2001, were 0.79 cases per 100 person-months, with 1.10 cases per 100 recruit-months during the winter months.

Of the 92 conjunctivitis cases, 80 (87%) were attributed to *S. pneumoniae;* 45 (49%) were confirmed cases, and 35 (38%) were probable cases. Other potential pathogenic organisms were identified in 12 cases (9 cases involving *H. influenzae,* 2 involving methicillin-susceptible *S. aureus,* and 1 involving adenovirus).

The mean age of patients infected with *S. pneumoniae* was 19.6 years (range, 17–27 years), which was not significantly different from that of patients with cases due to other etiologies or from the general recruit population. All cases occurred in persons with no significant medical problems, and none were currently taking antibiotics other the weekly doses of azithromycin. Most cases occurred during the first few weeks of training, with a median time of occurrence on day 14 of training (range, day 1–58). There were no statistically significant differences among the clinical characteristics of those with confirmed *S. pneumoniae* conjunctivitis, compared with those with conjunctivitis that had other etiologies (table 1). The median time of eye symptoms before presentation was 2 days (range, 1–24 days). The most common symptom among those with pneumococcal conjunctivitis was discharge, which was typically yellow; other signs and symptoms in descending order included itching, periorbital erythema, burning, swelling, pain, and periorbital edema. All patients were afebrile at the time of presentation.

Of the 17 patients with confirmed *S. pneumoniae* conjunctivitis who had a chest radiograph at the time of presentation, 4 (23.5%) had confirmed pneumonia; another patient was given the diagnosis of acute bacterial sinusitis. All 5 were treated

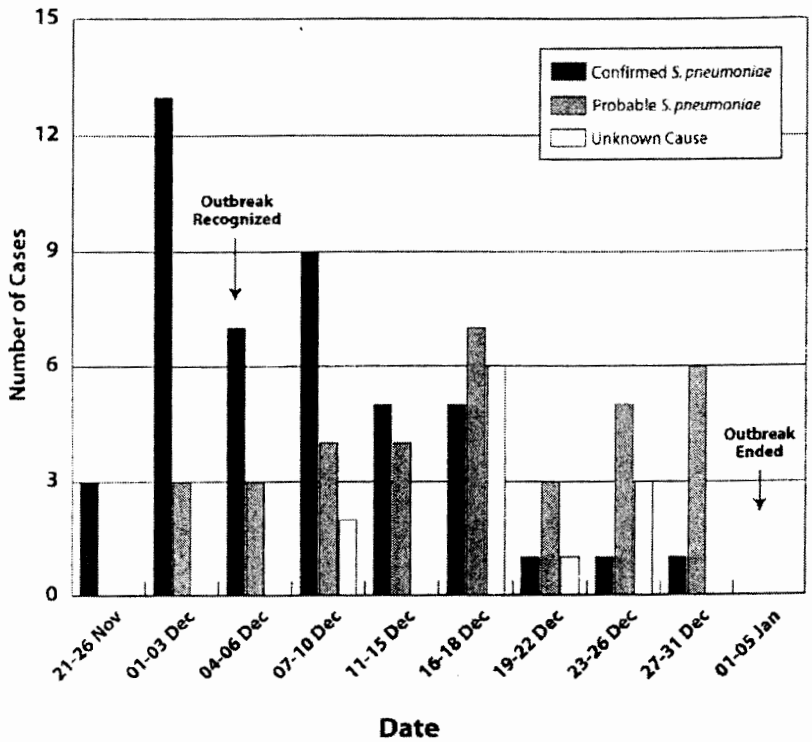

Figure 1. Epidemic curve for an outbreak of *Streptococcus pneumoniae* conjunctivitis, San Diego, 2003

with oral levofloxacin. Five (33.3%) of 15 patients had an elevated WBC count; 3 of these patients had normal chest radiograph findings, and examination revealed no source of infection except for conjunctivitis.

All isolates were unencapsulated and susceptible to clindamycin, tetracycline, levofloxacin, and vancomycin; 33 were susceptible to penicillin (MIC, <0.06 μg/mL), and 9 had intermediate resistance (MIC, 0.12 μg/mL). All isolates were resistant to trimethoprim-sulfamethoxazole. Macrolide testing revealed resistance to both erythromycin (MIC, >1 μg/mL) and azithromycin (MIC, 48–64 μg/mL), but all isolates were susceptible to telithromycin (>19 mm of zone inhibition by disk diffusion). Eleven isolates were genetically sequenced and found to have an identical allelic profile (*aroE*8, *gdh*10, *gki*4, *recP*1, *spi*2, *xpt*1, *ddl*71) by multilocus sequence typing. This profile was not previously reported in the large multilocus sequence typing database (http://www.mlst.net) of pneumococcal clones and was thus assigned a new sequence type, ST1186. This unique sequence type was then compared with those of other pneumococcal isolates from conjunctivitis outbreaks. The allelic profile of a pneumococcal isolate associated with a conjunctivitis outbreak at this same recruit camp in 1980 was found to be ST378; this profile was previously noted in the multilocus sequence typing database and was unique from outbreak clone, ST1186. Of interest, however, the closest associated *S. pneumoniae* type found in this database came from isolates from the recently described conjunctivitis outbreak at Dartmouth College (Hanover, NH) [4]. Figure 2 demonstrates this relationship, as well as a comparison of other conjunctivitis sequence types found in the multilocus sequence typing database.

All case patients with *S. pneumoniae* conjunctivitis, with 3 exceptions, received topical antimicrobial therapy at the initial presentation, which included polymyxin B–trimethoprim (22 case patients), erythromycin (19), ciprofloxacin (20), polymyxin B–bacitracin (10), polymyxin B (4), and gentamicin (2). Of those treated initially with erythromycin, 4 (21.1%) had persistent symptoms requiring a switch to another topical antimicrobial (ciprofloxacin), which resulted in clinical success; there was only 1 other clinical failure, which occurred in a patient initially treated with polymyxin B. Most erythromycin use occurred early in the outbreak before antimicrobial resistance to the macrolides was known.

The survey of 151 recruits (4.3%) performed in the group most affected demonstrated a carriage rate of 9.9% (15 recruits). These oropharyngeal isolates were genetically and phenotypically identical to the unencapsulated organisms in conjunctivitis cases, except that 2 were susceptible to trimethoprim-sulfamethoxazole. Of those with *S. pneumoniae* carriage, 26.7% had eye symptoms, compared with 21.3% among noncarriers (OR, 1.4; $P = .7$) (table 2). There were no statistically significant differences in demographic characteristics, clinical symptoms, or risk factors among those with and those without

Table 1. Characteristics of case patients during outbreak of conjunctivitis due to *Streptococcus pneumoniae*, 2003.

Characteristic	Cause of conjunctivitis					
	S. pneumoniae			Other pathogenic organisms		
	Confirmed (n = 45)	Probable (n = 35)	Total (n = 80)	(n = 12)	OR	P[a]
Age, mean years (range)	19.6 (17–27)	20 (18–25)	19.9 (17–27)	19.7 (18–24)	1.04	.7
Eye symptom						
Duration, median days (range)	2 (1–24)	2 (1–10)	2 (1–24)	1 (1–4)	1.3	.3
Discharge	96.7	88	92.7	71.4	5.1	.1
Colored discharge	92.6	94.4	93.3	80	3.5	.4
Eye pain	37.9	20.8	30.2	28.6	1.1	1.0
Itching	41.4	62.5	50.9	100	...	.06
Swelling	44.8	25	35.8	33.3	1.1	1.0
Burning	50.0	20.8	37	16.7	2.9	.4
Findings on examination						
Bilateral involvement	54.8	51.7	53.5	37.5	1.9	.5
Periorbital edema	30	18.2	25	0	...	.3
Periorbital erythema	37.9	59.1	47.1	16.7	4.4	.2
Cough	23.3	36	29.1	28.6	1.0	1.0
Radiographic pneumonia[b]	23.5	14.3	20.8	0	...	1.0
Elevated WBC count[b]	33	16.7	25.9	33.3	0.7	1.0
WBC count, mean cells $\times 10^3$ (range)	9.5 (5.7–15.2)	8.8 (5.1–12.1)	9.2 (5.1–15.2)	9.8 (8.2–10.9)	0.9	.5

NOTE. Data are percentage of case patients with characteristic, unless otherwise indicated.

[a] Comparison between *S. pneumoniae* conjunctivitis and conjunctivitis due to other pathogenic etiology.

[b] Chest radiography and WBC tests were performed on a subset of patients on the basis of a clinician's assessment.

S. pneumoniae carriage. A total of 33 (21.9%) of the 151 surveyed recruits reported a recent history of eye symptoms consistent with conjunctivitis. Those with conjunctivitis were more likely to share washcloths with other recruits (OR, 11.7; P = .03); there was a trend towards an association with wearing glasses (OR, 2.2; P = .09) and a history of contact with a recruit with conjunctivitis (OR, 2.2; P = .08).

DISCUSSION

We report a military training camp outbreak of conjunctivitis due to a novel *S. pneumoniae* strain. During the 6-week outbreak period, 92 cases of conjunctivitis occurred, with 80 (87%) due to *S. pneumoniae*, among 3500 military members (2.6% affected; rate of 1.75 cases per 100 person-months). The number of cases was likely underestimated, because a survey revealed that 22% of 1 training group self-reported symptoms consistent with conjunctivitis during the outbreak period. Ten percent of recruits surveyed carried the outbreak strain. The causative organism was a novel unencapsulated pneumococcal isolate.

Bacterial conjunctivitis manifests as abrupt ocular irritation and purulent discharge, often involving both eyes, and is caused by a wide range of gram-positive and -negative organisms [1]. Diagnosis is established by culture of eye secretions. Although *S. pneumoniae* is often the cause of sporadic conjunctivitis, outbreaks are uncommon [2] and have usually occurred among students [3, 4, 8]. The most recent outbreak occurred in February 2002 at Dartmouth College, with 698 cases of conjunctivitis over a 3-month period; 110 were proven to be due to *S. pneumoniae*. Analysis of the isolates showed an unencapsulated strain that was identical to previous outbreak strains in the 1980s [4]. An additional *S. pneumoniae* conjunctivitis outbreak in 2002 at an elementary school in Maine (101 cases, 11 of which were proven to be due to *S. pneumoniae*) was caused by a strain identical to the Dartmouth College outbreak strain [9]. Other outbreaks have included 1567 conjunctivitis cases among students in 7 colleges in New York State (1980), 294 cases in college students in New York (1981), and 1189 university students in Illinois (1981) [10].

Two prior outbreaks of *S. pneumoniae* conjunctivitis have occurred among military trainees. An outbreak at the same recruit training center in San Diego as our report occurred in September of 1980, resulting in 80 cases of conjunctivitis [10]. At the Great Lakes Navy Training Center in Illinois, 561 conjunctivitis cases were described over a 3-month period in 1996; 32 (33%) of the 97 samples cultured were positive for *S. pneumoniae* [11]. The outbreak reported here is unique because of the high rate of positive culture results and discovery of a new outbreak strain.

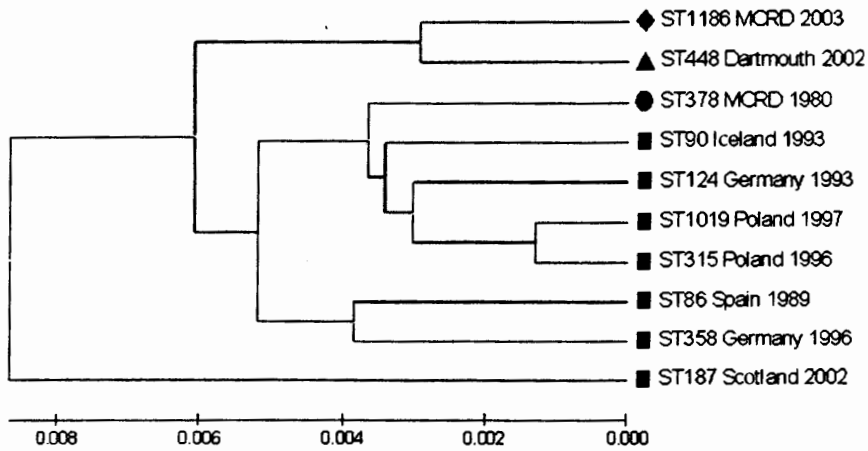

Figure 2. Genetic relatedness of pneumococcal sequence types by multilocus sequence typing associated with conjunctivitis cases. Linkage distance is shown at bottom. Data for isolates indicated with solid square or triangle were obtained from multilocus sequence typing database (http://www.mlst.net). *Solid diamond,* outbreak clone; *solid circle,* pneumococcal isolate from 1980 outbreak at same recruit camp.

As demonstrated in figure 2, pneumococci causing conjunctivitis are diverse. This diversity is consistent with the known epidemic population structures that exist because of the frequency of recombination events in pneumococci [12, 13]. We did observe a close relationship between our outbreak strain and the sequence type observed in the outbreak clone identified in the Dartmouth College investigation [4]. Furthermore, our strain also shares similarities with the Dartmouth clone in erythromycin resistance patterns observed and lack of encapsulation.

Recently reported *S. pneumoniae* isolates from conjunctivitis outbreaks are unencapsulated and, thus, nontypeable [11, 14–16]. Most *S. pneumoniae* isolates recovered from other body sites are encapsulated [4, 10]; the capsule serves as a major pathogenic factor for invasive disease by preventing phagocytosis. Because conjunctivitis is a superficial process, the presence of a capsule is not necessary for infection. In fact, some studies have suggested that unencapsulated pneumococci may be more adherent to mucosal surfaces than are those containing a capsule [16–18]. Pneumococci usually reach the conjunctiva from the nasopharynx, after exposure of respiratory droplets, or by direct contact [19]; the tropism for the conjunctiva may be related to the lack of antibodies and complement in this environment [11]. Adhesins and surface proteins, such as pneumococcal surface adhesion A, surface protein C, and choline-binding protein A, are important for surface attachment [20]. After adhesion to the conjunctival surface, production of cytolysin may play a role in the development of conjunctivitis, as demonstrated in animal models [19]. The precise pathogenesis by which encapsulated pneumococci cause conjunctivitis requires further study.

The clinical manifestations of *S. pneumoniae* in our outbreak were typical, with mucopurulent discharge being the most commonly reported symptom. More than one-half of the case patients had bilateral involvement at initial presentation; the organism frequently involves the other eye within the first 48 h of illness [1]. Of note, 4 of our case patients with confirmed *S. pneumoniae* conjunctivitis had concurrent pneumonia at the time of diagnosis. No other pathogens were isolated; thus, it is unclear whether the outbreak isolate played a role in these invasive infections. There have been no reports of unencapsulated pneumococci causing pneumonia. All conjunctivitis cases had uncomplicated resolution; this is consistent with the literature, suggesting that cases are self-limited and typically resolve within 1 week [19]. Nonetheless, use of a topical antibiotic has been shown to shorten the duration of clinical disease and enhance organism eradication [21]. In this outbreak, 21% of case patients receiving topical erythromycin returned to the clinic with continued symptoms and were successfully treated with topical ciprofloxacin.

All *S. pneumoniae* isolates recovered from patients with conjunctivitis had similar antibiograms. Of interest, all isolates were resistant to erythromycin and azithromycin but susceptible to the new ketolide, telithromycin. These data are consistent with studies showing improved efficacy of telithromycin against pneumococcal isolates [22–25]. Two months before the outbreak, azithromycin replaced benzathine penicillin for prevention of respiratory and group A streptococcal infections and was administered to all 3500 military trainees on a weekly basis. This change in antibiotic prophylaxis was in response to increasing cases of pneumonia predominantly due to atypical pathogens, including *Mycoplasma pneumoniae* and *Chlamydia pneumoniae;* studies had previously shown the utility of azithromycin in this situation [26–28]. The use of azithromycin may have created selective pressure towards macrolide-resistant pneumococci in the camp [29]. Of interest, most isolates were

Table 2. Characteristics, symptoms, and risk factors of persons with and those without pharyngeal carriage of *Streptococcus pneumoniae* and with and without cases of conjunctivitis during outbreak, 2003.

Characteristic	Patients with *S. pneumoniae* carriage (n = 15)	Patients without *S. pneumoniae* carriage (n = 136)	OR[a]	P[a]	Patients with self-reported conjunctivitis (n = 33)	Asymptomatic persons (n = 118)	OR[b]	P[b]
Age, mean years (range)	19.5 (18–23)	19.7 (18–26)	0.9	.89	19.9 (18–22)	19.6 (18–26)	1.1	.11
White race	10 (66.7)	86 (63.2)	1.2	.98	22 (66.7)	74 (62.7)	1.2	.83
Eye infection								
Symptoms consistent with conjunctivitis	4 (26.7)	29 (21.3)	1.3	.74	33 (100)	...	...	...
Duration of conjunctivitis, median days (range)	2 (1–3)	3 (1–10)	0.3	.08	3 (1–10)	...	...	...
Missed work because of conjunctivitis	1 (6.7)	3 (2.2)	3.2	.34	4 (12.1)	0	...	.002[c]
Other symptom								
Fever	0	10 (7.4)	...	.60	2 (6.1)	8 (6.8)	0.9	1.0
Cough	8 (53.3)	73 (53.7)	1.0	.80	21 (63.6)	60 (50.8)	1.9	.20
Sore throat	4 (26.7)	44 (32.4)	0.8	.76	10 (30.3)	38 (32.2)	0.92	1.0
Risk factor								
Contact with person with conjunctivitis	7 (46.7)	53 (39)	1.4	.76	18 (54.5)	42 (35.6)	2.2	.08
Sharing towels	1 (6.7)	0	...	.10	1 (3)	0	...	.22
Sharing washcloths	0	4 (2.9)	...	1.0	3 (9.1)	1 (0.8)	11.7	.03[c]
No use of soap	2 (13.3)	4 (2.9)	5.1	.11	1 (3)	5 (4.2)	0.7	1.0
No use of liquid hand cleaner	0	0	...	...	0	0	...	...
Cigarette use in past 6 months	4 (26.7)	54 (39.7)	0.6	.48	16 (48.5)	42 (35.6)	1.7	.25
Wearing glasses	6 (40)	42 (30.9)	1.5	.56	15 (45.5)	33 (28)	2.2	.09

NOTE. Data are no. (%) of persons, unless otherwise indicated.

[a] For patients with *S. pneumoniae* carriage vs. patients without *S. pneumoniae* carriage.

[b] For patients with self-reported conjunctivitis vs. asymptomatic persons.

[c] Statistically significant (P < .05).

susceptible to penicillin; reports of ocular infections due to penicillin-resistant *S. pneumoniae* have been noted [30].

The outbreak was controlled through education about good hygienic practices, including avoiding sharing washcloths, increasing hand washing, and using alcohol-based gels. Alcohol-based gels have been useful in controlling other conjunctivitis outbreaks, but a formal study of their utility in this setting is lacking [4]; their usefulness has been proven in hospital settings [31]. Another component in the control of the outbreak was likely the reduction of the number of military trainees at the camp, which serendipitously occurred during the holiday season. It is unclear which, if any, of these preventive strategies were important in halting the outbreak. Pneumococcal immunization was not useful in this outbreak; although the 23-valent polysaccharide vaccine has excellent efficacy in preventing pneumococcal bacteremia in adults, it has no significant benefit in preventing surface infections, such as conjunctivitis, otitis media, or pneumonia [32, 33]. Furthermore, the antibody response generated is to that of capsular polysaccharides; however, the outbreak strain was unencapsulated. A better understanding of the pathogenesis of pneumococcal infections [20], particularly those due to unencapsulated strains, is needed to devise improved preventive strategies.

Acknowledgments

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Conflict of interest. All authors: No conflict.

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14. ABSTRACT (maximum 200 words)

Context: Bacterial conjunctivitis usually occurs as sporadic cases; outbreaks are uncommon and usually are associated with school campuses. We report an outbreak of conjunctivitis due to a novel *Streptococcus pneumoniae* strain that occurred among military trainees.
Objective: An outbreak investigation was begun to determine the extent of the outbreak, confirm the cause, and implement preventive strategies.
Results: During a 6-week period, 92 cases of conjunctivitis occurred among 3500 persons, with an overall attack rate of 1.75 cases per 100 person-months. Eighty (87%) cases were due to *S. pneumoniae*; 45 (49%) were confirmed cases, and 35 (38%) were probable cases. Ten percent of recruits surveyed carried the outbreak strain. Twenty-two percent self-reported symptoms consistent with conjunctivitis during the outbreak period; sharing washcloths was associated with conjunctivitis (odds ratio=11.8, p=0.03). The causative organism was resistant to azithromycin, but sensitive to telithromycin. The outbreak strain was identified as an unencapsulated *S. pneumoniae* that has not previously been described; it was most closely related to the sequence type causing the Dartmouth College outbreak in 2002.
Conclusions: This outbreak of bacterial conjunctivitis among military trainees was caused by a novel, unencapsulated strain of *S. pneumoniae*.

15. SUBJECT TERMS
Streptococcus pneumoniae, conjunctivitis, ocular infection, military, outbreak

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